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REMARKS

Claims 1-3, 6-9, 11-13, 17-18, and 26-37 are pending and under consideration. Claims 13 and 26 and the specification have been amended merely to include sequence identifiers. Additionally, the specification has been amended to correct a typographical error and to accompany registered trademarks with the ® symbol as requested by the Examiner. The abstract and title have been amended to more adequately describe the claimed invention as requested by the Examiner. Claims 1 and 12 have also been amended. Support for these amendments can be found throughout the specification, for example, on page 3, lines 28-36; page 7, lines 10-12; and in the claims as originally filed. No new matter has been added. Please consider the following remarks.

Requirements under 37 C.F.R. §1.85

Figures 7-12 are objected to because of a number of informalities. A transmittal of formal drawings with the appropriate corrections is being filed herewith.

Rejections under U.S.C. § 102

Claims 1-3, 10, 26, and 27 are rejected under 35 U.S.C. § 102(e) as being anticipated by Wayner et al. (U.S. Patent No. 5,730, 978) ("Wayner"). Wayner discloses the use of fibronectin fragments to treat asthma. This rejection has been overcome by narrowing the pending independent claims 1 and 12 to recite the identification and treatment of allergic asthma. Wayner does not disclose the treatment of allergic asthma, but rather only refers to asthma in general. The general term "asthma" encompasses at least two different asthmatic disorders, namely allergic asthma, as claimed, and non-allergic asthma. At the time of the priority date of the application, these two forms were known to exist as clinically distinct disorders having different incidences, etiologies and prognoses, as evidenced by the enclosed sections of Dorland's Illustrated Medical Dictionary (1988) and the Merck Manual of Diagnosis and Therapy (1987). Thus, the skilled person would understand the term "asthma," as used in Wayner, to refer to a genus of related, but distinct disorders. A mention of the treatment of

asthma in general cannot be said to anticipate the treatment of allergic asthma, as claimed. Accordingly, Wayner does not anticipate the present claims.

In a second aspect of this rejection, claims 1-3, 10, 26, and 27 are rejected under 35 U.S.C. § 102(e) as being anticipated by Kogan et al. (U.S. Patent No. 5,520,332) ("Kogan"). Similarly to Wayner, Kogan discloses methods for the treatment of asthma, but does not disclose or suggest treatment of the specific type of asthma recited in the claims as amended, i.e., allergic asthma. For the reasons discussed above with regard to Wayner, a mention of the treatment of asthma in general cannot be said to anticipate the treatment of allergic asthma, as claimed. Thus, the presently pending claims are not anticipated by Kogan.

In yet another aspect of this rejection, claims 1-3, 6, 7, 10, 26 and 27 are rejected under 35 U.S.C. § 102(e) as being anticipated by Arrhenius et al. (U.S. Patent No. 6,117,840) ("Arrhenius"). Arrhenius discloses the use of small molecules that are highly modified CS-1 peptidomimetic inhibitors to treat asthma. These inhibitors are peptides modified with amide ring-containing groups at both the N- and C- terminus (see columns 8-9 and Table 1 of Arrhenius). Thus, the Arrhenius inhibitors cannot be said to be fibronectin polypeptides, as claimed. Therefore, Arrhenius does not anticipate the present claims.

Rejections under U.S.C. § 103

Claims 1-3, 7, 9-13, 17, 18, and 26-37 are rejected under U.S.C. § 103(a) as being unpatentable over Wayner and/or Kogan and/or Arrhenius in view of art known of the nature and treatment of asthma at the time the invention was made. This rejection is respectfully traversed.

To establish prima facie obviousness of a claimed invention, "the prior art reference (or references when combined) must teach or suggest all the claim limitations" (see MPEP § 706.02(j), emphasis added). In addition, there must be a motivation to combine or modify the reference(s) to arrive at the claimed invention, and a reasonable expectation of success. Here, a prima facie case of obviousness has not been made because the cited references lack a teaching, suggestion or motivation to perform the claimed methods. For the reasons outlined above, none of these references teaches administration of a soluble fibronectin polypeptide to a patient suffering from allergic asthma. Furthermore, the Examiner has provided no evidence of a suggestion to modify the references (alone or in combination) or a reasonable expectation of

success to arrive at the claimed methods. Indeed, Wayner and Kogan provide only in-vitro experiments. While in-vitro data can serve to characterize a biochemical pathway, one of skill in the art would look only to in vivo data to identify the crucial roles of adhesion molecule in a human pathology. Therefore, neither Wayner nor Kogan provide a motivation or reasonable expectation of success for an ordinary artisan to arrive at the claimed methods. Nor does Arrhenius make up for this deficiency. While Arrhenius discloses in vivo data with highly modified peptidomimetic agents, Arrhenius does not disclose or suggest administering soluble fibronectin polypeptides, as required by the claims. In fact, Arrhenius teaches away from fibronectin polypeptides, such as CS-1 peptides, by describing their drawbacks. For example, at column 4:54-56 of Arrhenius (the background section), it is stated that the CS-1 peptide "is large and costly to make, and also is subject to rapid degradation." Thus, a skilled artisan would have been led away from the present invention by Arrhenius. Accordingly, a prima face case of obviousness has not been made and Applicants respectfully request that the rejection be withdrawn.

Attached is a marked-up version of the changes being made by the current amendment.

Applicant asks that all claims be allowed. Enclosed is a check for the requisite fees. Please apply any other charges or credits to Deposit Account No. 06-1050, referencing attorney docket number 10274-003003.

Respectfully submitted,

Date: 24 January 2003

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Version with markings to show changes made

In the specification:

Paragraph beginning at page 1, line 7 has been amended as follows:

-- This application is a continuation of USSN 09/822,830, now U.S. Patent No. 5,871,734, which is a continuation-in-part of Lobb USSN 08/374,331, filed January 18, 1995, now abandoned, which is a continuation-in-part of Lobb USSN 08/256,631, filed July 12, 1994, now abandoned, and of PCT/US93/00030 filed January 12, 1993, which is the continuation of part of Lobb 07/821,786, now abandoned, filed January 13, 1992, all of which are hereby incorporated by reference. --

Paragraph beginning at page 10, line 7 has been amended as follows:

-- As discussed herein, the blocking agents used in methods of the invention are not limited to antibodies or antibody derivatives, but may be other molecules, e.g., soluble forms of other proteins which bind VLA-4, e.g., the natural binding proteins for VLA-4. These binding agents include soluble VCAM-1 or VCAM-1 peptides, VCAM-1 fusion proteins, bifunctional VCAM-1/Ig fusion proteins, fibronectin, fibronectin having an alternatively spliced non-type III connecting segment, and fibronectin peptides containing the amino acid sequence EILDV (SEQ ID NO.:16) or a similar conservatively substituted amino acid sequence. These binding agents can act by competing with the cell-surface binding protein for VLA-4 or by otherwise altering VLA-4 function. For example, a soluble form of VCAM-1 (see, e.g., Osborn et al. 1989 [18]) or a fragment thereof may be administered to bind to VLA-4, and preferably compete for a VLA-4 binding site, thereby leading to effects similar to the administration of anti-VLA-4 antibodies. Soluble VCAM-1 fusion proteins can be used in the methods described herein. For example, VCAM-1, or a fragment thereof which is capable of binding to VLA-4 antigen on the surface of VLA-4 bearing cells, e.g., a fragment containing the two N-terminal domains of VCAM-1, can be fused to a second peptide, e.g., a peptide which increases the solubility or the in vivo life time of the VCAM-1 moiety. The second peptide can be a fragment of a soluble peptide, preferably a human peptide, more preferably a plasma protein, or a member of the immunoglobulin super

family. In particularly preferred embodiments, the second peptide is IgG or a portion or fragment thereof, e.g., the human IgG1 heavy chain constant region. A particularly preferred fusion protein is the VCAM 2D-IgG fusion. --

Paragraph beginning at page 10, line 35 has been amended as follows:

-- In another aspect the invention features a chimeric molecule which includes: (1) a VLA-4 targeting moiety, e.g., a VCAM-1 moiety capable of binding to a VLA-4 antigen on the surface of VLA-4 bearing cells; (2) optionally, a second peptide, e.g., one which increases solubility or in vivo life time of the VLA-4 targeting moiety, e.g., a member of the immunoglobulin super family or fragment or portion thereof, e.g., a portion or a fragment of IgG, e.g., the human IgG1 heavy chain constant region, e.g., CH2 and CH3 hinge regions; and (3) a toxin moiety. The VLA-4 targeting moiety can be any naturally occurring VLA-4 ligand or fragment thereof, e.g., a VCAM-1 peptide, fibronectin, fibronectin having an alternatively spliced non-type III connecting segment, and fibronectin peptides containing the amino acid sequence EILDV (SEQ ID NO.:16) or a similar conservatively substituted amino acid sequence. A perferred targeting moiety is a soluble VCAM-1 fragment, e.g., the N-terminal domains 1 and 2 of the VCAM-1 molecule. The toxin moiety can be any agent which kills or inactivates a cell when the toxin in targeted to the cell by the VLA-4 targeting moiety. Toxin moieties include: cytotoxic peptide moieties, e.g., Diphtheria toxin A, *Pseudomonas* Exotoxin, Ricin A, Abrin A, *Schigella* toxin, or Gelonin; radionucleiotides; and chemotherapeutic agents. --

Paragraph beginning at page 10, line 7 has been amended as follows:

-- Experiments were performed essentially as described by Abraham et al. [8]. Briefly, allergic sheep having natural allergic cutaneous reaction to 1:1000 or 1:10,000 dilutions of Ascaris suum extract (Greer Diagnostics, Lenoir, N.C.) were tested, and sheep demonstrating both early and late phase airway response ("dual responders") to inhalation challenge with Ascaris suum antigen were selected. To measure breathing mechanics and physical changes in the airways, the sheep were restrained in a prone position with heads immobilized. A balloon catheter was advanced through one nostril under topical anesthesia with 2% lidocaine solution to the lower esophagus, and a cuffed endotracheal tube was advanced through the other nostril

(using a flexible fiberoptic bronchoscope as a guide) for the measurement of airway mechanics and during aerosol challenges. Pleural pressure was estimated with the esophageal balloon catheter (filled with 1 ml of air) positioned 5-10 cm from the gastroesophageal junction. In this position, end expiratory pleural pressure ranged between -2 and -5 cm H_2O. Once the balloon was placed, it was secured so that it remained in position for the duration of the experiment. Lateral pressure in the trachea was measured with a sidehole catheter, (inner diam. 2.5 mm) advanced through and positioned distal to the tip of the endotracheal tube. Transpulmonary pressure (the difference between tracheal and pleural pressure) was measured with a differential pressure transducer catheter system (MP45, Validyne, Northridge, Calif.). The pressure transducer catheter system showed no phase shift between pressure and flow to a frequency of 9 H_z. Pulmonary resistance (R_L) was measured by connecting the proximal end of the endotracheal tube to a [Fleich]Fleisch pneumotachograph (Dyna Sciences, Blue Bell, Pa.). Signals indicating flow and transpulmonary pressure were recorded on an oscilloscope recorder (Model DR-12; Electronics for Medicine, White Plains, N.Y.) linked to a computer for automatic calculation of pulmonary resistance (R_L) from transpulmonary pressure, respiratory volume (obtained by digital integration) and flow by the mid-volume technique, analyzed from 5-10 breaths. Thoracic gas volume (V_{tg}) was measured immediately after determination of R_L in a constant volume body plethysmograph. Specific lung resistance (SR_L) was calculated from these values (SR_L =Vtg x R_L). --

Paragraph beginning at page 19, line 16 has been amended as follows:

-- Wells of Immulon 2® plates (Dynatech, Chantilly, Va.) were each coated with anti-VCAM MAb 4B9 (isolated and purified on Protein A Sepharose as described by Carlos et al, 1990 ›56!) with 100 .mu.l of anti-VCAM 4B9 MAb diluted to 10 µg/ml in 0.05M sodium carbonate/bicarbonate buffer, pH 9.6, covered with Parafilm® (thin sealing film), and incubated overnight at 4°C. The next day, the plate contents were dumped out and blocked with 200 µl/well of a block buffer (5% fetal calf serum in 1.times. PBS), which had been filtered through a 2 filter. The buffer was removed after a 1 hour incubation at room temperature and the plates were washed twice with a solution of 0.05% Tween-20 in 1XPBS. Conditioned medium was added at various dilutions. As a positive control, an anti-mouse Ig was also included. Block buffer and

LFA-3TIP constituted as negative controls. The samples and controls were incubated at room temperature for 2 hours. --

Paragraph beginning at page 20, line 9 has been amended as follows:

-- CHO cells expressing VCAM 2D-IgG were grown in roller bottles on collagen beads. Conditioned medium (5 Liters) was concentrated to 500 ml using an Amicon® S1Y10 spiral ultrafiltration cartridge (Amicon, Danvers, Mass.). The concentrate was diluted with 1 liter of Pierce Protein A binding buffer (Pierce, Rockford, Ill.) and gravity loaded onto a 10 ml Protein A column (Sepharose® 4 Fast Flow, Pharmacia, Piscataway, N.J.). The column was washed 9 times with 10 ml of Protein A binding buffer and then 7 times with 10 ml of PBS. VCAM 2D-IgG was eluted with twelve-5 ml steps containing 25 mM H_3P0_4 pH 2.8, 100 mM NaCl. The eluted samples were neutralized by adding 0.5M Na_2HP0_4 pH 8.6 to 25 mM. Fractions were analyzed for absorbance at 280 nm and by SDS-PAGE. The three peaks fractions of highest purity were pooled, filtered, aliquoted and stored at -70°C. By SDS-PAGE, the product was greater than 95% pure. The material contained less than 1 endotoxin unit per mg of protein. In some instances, it was necessary to further purify the Protein A eluate product on Q-Sepharose® FF (Pharmacia). The protein A eluate was diluted with 3 volumes of 25 mM Tris HCl pH 8.0 and loaded onto a Q-Sepharose® FF column at 10 mg VCAM 2D-IgG per ml of resin. The VCAM 2D-IgG was then eluted from the Q- Sepharose® with PBS. --

In the claims:

Claims 1, 12, 13 and 26 have been amended as follows:

1. A method for the treatment of allergic asthma comprising:
identifying a mammal suffering from allergic asthma; and
administering to [a]the mammal [suffering from asthma] a composition comprising a soluble fibronectin polypeptide.

12. A method for the treatment of allergic asthma comprising:
identifying a mammal suffering from allergic asthma; and

administering to [a]the mammal [suffering from allergic asthma] a soluble fibronectin polypeptide capable of binding to the α4 subunit of VLA-4, in an amount effective to provide inhibition of late phase response to an allergen to which the sufferer is hypersensitive or to provide decreased airway hypersensitivity in said mammal following allergen challenge.

13. The method of Claim 12, wherein the soluble fibronectin polypeptide comprises an EILDV motif (SEQ ID NO.: 16).

26. The method according to Claim 1, wherein the soluble fibronectin polypeptide comprises an EILDV motif (SEQ ID NO.: 16).

In the abstract:

The abstract has been amended as follows:

-- A method for the treatment of allergic asthma is disclosed. The method comprises administering to a mammal a composition including a soluble fibronectin polypeptide [administration of an antibody, polypeptide or other molecule recognizine VLA-4, a protein expressed on the surface of certain leukocytes such as eosinophils]. --

27th Edition

DORLAND'S ILLUSTRATED

Medical Dictionary

1988
W.B. SAUNDERS COMPANY
Harcourt Brace Jovanovich, Inc.
Philadelphia London Toronto
Montreal Sydney Tokyo

astaxanthin (as"tah-zan'thin) a red carotenoid pigment, $C_{40}H_{52}O_4$, constituent of the green chromoprotein from the eggs of crayfish.

asteatodes (as"te-ah-to'dēz) asteatosis.

asteatosis (as"te-ah-to'sis) [a neg. + Gr. *stear* tallow + -osis] any disease characterized by such persistent fine dry scaling of the skin surface as to suggest scantiness or absence of the sebaceous secretion. Called also *asteatodes*. See also *chapping*; *winter itch*, under *itch*; and *xerotic eczema*, under *eczema*.

aster (as'ter) [L.; Gr. *astēr* star] a structure seen in a cell during the prophase of mitosis, composed of a system of microtubules arranged in astral rays around the centrosome; called also *astrosphere*, *cytaster*, and *kinosphere*. **sperm a.**, the centriole, with astral rays, that precedes the male pronucleus during fertilization.

astereocognosy (ah-ste"re-o-kog'nō-se) astereognosis.

astereognosis (ah-ster"e-og-no'sis) [a neg. + Gr. *stereos* solid + *gnōsis* recognition] loss of power to recognize objects or to appreciate their form by touching or feeling them; called also *tactile amnesia*.

asterion (as-te're-on), pl. *aste'ria* [Gr. "starred"] [NA] the point on the surface of the skull where the lambdoid, parietomastoid, and occipitomastoid sutures meet.

asterixis (as"ter-ik'sis) [a neg. + Gr. *stērixis* a fixed position] a motor disturbance marked by intermittent lapse of an assumed posture, as a result of intermittency of the sustained contraction of groups of muscles, a characteristic of hepatic coma but observed also in numerous other conditions; called also *liver flap* and *flapping tremor*.

asternal (a-ster'nal) 1. not joined to the sternum. 2. pertaining to asternia; lacking a sternum.

asternia (ah-ster'ne-ah) [a neg. + Gr. *sternon* sternum + -ia] congenital absence of the sternum.

Asterococcus (as"ter-o-kok'us) in former systems of classification, a genus of bacteria of the order Mycoplasmatales, the organisms of which have been assigned to the genera *Acholeplasma* and *Mycoplasma*.

asteroid (as'ter-oid) [Gr. *astēr* star + *eidos* form] star-shaped; resembling the aster.

Asterol (as'ter-ol) trademark for preparations of diamthazole dihydrochloride.

asterubin (as"te-roo'bin) a basic substance, $NH{:}C(NH_2)\cdot CH_2\cdot SO_2OH)\cdot N(CH_3)_2$, that has been isolated from the starfish.

Asth. asthenopia.

asthenia (as-the'ne-ah) [Gr. *asthenēs* without strength + -ia] lack or loss of strength and energy; weakness. **myalgic a.**, a condition in which the general symptoms are a sensation of general fatigue and muscular pains. **neurocirculatory a.**, a syndrome characterized by palpitations, dyspnea, a sense of fatigue, fear of effort, and discomfort brought on by exercise or even slight effort; considered by most authorities to be a particular presentation of anxiety neurosis (anxiety state), the physical symptoms being attributed to autonomic responses to anxiety or to hyperventilation. Called also *DaCosta's syndrome*, *disordered action of the heart*, *effort syndrome*, *functional cardiovascular disease*, and *irritable heart* or *soldier's heart*. **periodic a.**, a condition marked by periodically returning attacks of marked asthenia. **tropical anhidrotic a.**, a rare condition occurring under conditions of heat stress, in which miliaria profunda causes extensive occlusion of the sweat ducts, producing anhidrosis and heat retention that may lead to weakness, dyspnea, tachycardia, elevation of body temperature, and collapse. Called also *sweat retention syndrome* and *thermogenic anhidrosis*.

asthenic (as-then'ik) pertaining to or characterized by asthenia.

asthen(o)- [Gr. *asthenēs* weak; from a- neg. + *sthenos* strength] a combining form denoting lack of strength or weakness.

asthenobiosis (as-the"no-bi-o'sis) [*asthenia* + Gr. *bios* life + -osis] a condition of reduced biologic activity resembling hibernation or estivation but not directly related to or dependant on temperature or humidity.

asthenocoria (as-the"no-ko're-ah) [*asthenia* + Gr. *korē* pupil + -ia] a condition in which the pupillary light reflex is sluggish; seen in hypoadrenalism. Called also *Arroyo's sign*.

asthenope (as'then-ōp) a person affected with asthenopia.

asthenophobia (as"thē-no-fo'be-ah) [*asthenia* + *phobia*] (obs.) irrational fear of being weak.

asthenopia (as"thē-no'pe-ah) [*asthenia* + -opia] weakness or easy fatigue of the visual organs, attended by pain in the eyes, headache, dimness of vision, etc. Previously a diagnostic term; now used mainly as a descriptive term. **accommodative a.**, asthenopia due to strain of the ciliary muscle. **hysterical a.**, functional asthenopia due to neurosis or psychosis. **muscular a.**, that which is due to weakness of the external ocular muscles. **nervous a.**, 1. hysterical a. 2. that due to organic nervous disease. **neurasthenic a.**, 1. that due to neurasthenia after an organic disease; called also *retinal a.* 2. *hysterical a.* **retinal a.**, neurasthenic a., def. 1. **tarsal a.**, asthenopia due to irregular astigmatism produced by the pressure of the lids on the cornea.

asthenopic (as"thē-nop'ik) characterized by asthenopia.

asthenospermia (as"thē-no-sper'me-ah) [*asthenia* + Gr. *sperma* seed + -ia] reduction in the vitality of spermatozoa.

asthenoxia (as"then-ok'se-ah) [*asthenia* + *oxygen*] lack of power to oxidize waste products.

asthma (az'mah) [Gr. *asthma* panting] a condition marked by recurrent attacks of paroxysmal dyspnea, with wheezing due to spasmodic contraction of the bronchi. Some cases of asthma are allergic manifestations in sensitized persons (*bronchial allergy*); others are provoked by a variety of factors, including vigorous exercise, irritant particles, psychologic stresses, etc. **abdominal a.**, asthma due to upward pressure on the diaphragm. **allergic a.**, bronchial asthma due to allergy; called also *atopic a.* **alveolar a.**, that which is characterized by dilatation of the alveoli of the lungs. **atopic a.**, allergic asthma. **bacterial a.**, asthma due to bacterial infection. **bronchial a.**, see *asthma*. **bronchitic a.**, asthmatic disorder accompanying bronchitis. **cardiac a.**, paroxysmal dyspnea that occurs in association with heart disease, such as left ventricular failure; called also *cardiasthma*. **cat a.**, asthma brought on by inhalation of cat dander by a sensitized person. **catarrhal a.**, bronchitic a. **a. convulsi'vum**, bronchial a. **cotton-dust a.**, byssinosis. **cutaneous a.**, reflex asthma believed to be caused by some irritation of the skin. **diisocyanate a.**, isocyanate a. **dust a.**, asthma caused by inhalation of dust. **Elsner's a.**, angina pectoris. **emphysematous a.**, emphysema of the lungs attended with asthmatic paroxysms. **essential a.**, asthma of unknown or inapparent cause; called also *true a.* **extrinsic a.**, asthma caused by some factor in the environment, usually allergic asthma. **food a.**, asthma brought on by ingestion of certain foods to which the person is allergic. **grinders' a.**, asthmatic symptoms related to the inhalation of fine particles set free in the grinding of metals. **Heberden's a.**, angina pectoris. **horse a.**, a form of allergic asthma in which the attacks are brought on by the presence of horses or of horse products. **humid a.**, asthma with profuse expectoration. **infective a.**, asthma due to infection. **intrinsic a.**, asthma attributed to pathophysiologic disturbances and not to environmental factors. **isocyanate a.**, bronchial asthma caused by allergy to toluene diisocyanate and similar materials. **Kopp's a.**, laryngismus stridulus. **Millar's a.**, laryngismus stridulus. **millers' a.**, a condition of the lungs found in millers, caused by the inhalation of cereal dusts. **miners' a.**, asthma associated with anthracosis. **nasal a.**, asthma caused by a disease of the nose. **nervous a.**, essential asthma, usually associated with emotional disturbances. **pollen a.**, hay fever. **potters' a.**, asthmatic symptoms associated with the pneumoconiosis of workers in the ceramic industries. **reflex a.**, asthma attributed to some reflex action. **Rostan's a.**, cardiac a. **sexual a.**, asthma resulting from sexual intercourse. **spasmodic a.**, bronchial a. **steam-fitters' a.**, asthmatic symptoms associated with asbestosis. **stone a.**, asthmatic symptoms due to broncholithiasis. **stripper's a.**, asthmatic symptoms associated with byssinosis. **symptomatic a.**, asthma that is secondary to some other physical condition. **thymic a.**, an alleged condition occurring usually in children, associated with enlargement of the thymus, paroxysmal attacks of asthma, and a tendency to sudden death. **true a.**, essential asthma. **Wichmann's a.**, laryngismus stridulus.

asthmatic (as-mat'ik) [L. *asthmaticus*] pertaining to or affected with asthma.

D30

FIFTEENTH EDITION

THE MERCK MANUAL

OF

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ventilator settings are then based on ABGs and patient comfort. Sedative drugs or narcotics may improve patient comfort and promote ventilator synchrony during mechanical ventilation. PEEP is usually required to maintain oxygenation while slowly decreasing the F_{IO_2}. An $F_{IO_2} > 0.50$ for longer than 24 to 48 h may be toxic and accentuate the lung injury. An arterial P_{O_2} of 60 to 70 mm Hg ensures adequate Hb saturation, and should be the goal of therapy. Using this goal, and carefully adjusting PEEP, it is usually possible to reduce the F_{IO_2} slowly to a level < 0.50 within a few hours. PEEP of 5 to 10 cm of H_2O is usually adequate, but ≥ 15 cm may be required. PEEP may depress the CO in hypovolemic patients. Correction of hypovolemia is essential. Secondary multiple organ system failure may be unwittingly advanced by systemic hypoperfusion resulting from the combination of volume depletion and PEEP.

Weaning readiness is based on continued evidence of improved lung function, shown by a decreasing need for O_2 and PEEP, improvement of x-ray findings, and resolution of tachypnea. In patients without previous underlying lung disease, weaning can usually be accomplished smoothly; difficulty in weaning may indicate an untreated or new site of infection, overhydration, bronchospasm, or poor nutritional status causing respiratory muscle weakness. If these factors are recognized and treated, successful weaning can usually be accomplished either by decreasing the mechanical rate using intermittent mechanical ventilation or by trials of spontaneous breathing of progressively longer duration using a T-piece attached to the endotracheal tube.

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36. AIRWAYS OBSTRUCTION

BRONCHIAL ASTHMA

A reversible obstructive lung disorder characterized by increased responsiveness of the airways.

Etiology

Bronchial asthma can occur secondarily to a variety of stimuli. The underlying mechanisms are unknown, but inherited or acquired imbalance of adrenergic and cholinergic control of airways diameter has been implicated (see Pathophysiology and Pathology, below). Persons manifesting such imbalance have hyperreactive bronchi and, even without symptoms, bronchoconstriction may be present. Overt asthma attacks may occur when such persons are subjected to various stresses, such as viral respiratory infection, exercise, emotional upset, nonspecific factors (eg, changes in barometric pressure or temperature), inhalation of cold air or irritants (eg, gasoline fumes, fresh paint and noxious odors, or cigarette smoke), exposure to specific allergens, and ingestion of aspirin or sulfites in sensitive individuals. Psychologic factors may aggravate an asthmatic attack but are not assigned a primary etiologic role.

Persons whose asthma is precipitated by allergens (most commonly airborne pollens and molds, house dust, animal danders) and whose symptoms are IgE-mediated are said to have allergic or "extrinsic asthma." They account for about 10 to 20% of adult asthmatics; in another 30 to 50%, symptomatic episodes seem to be triggered by nonallergenic factors (eg, infection, irritants, emotional factors), and these patients are said to have nonallergic or "intrinsic asthma." In many persons, both allergenic and nonallergenic factors are significant. Allergy is said to be a more important factor in children than in adults, but the evidence is inconclusive.

Pathophysiology and Pathology

Asthmatic attacks are characterized by narrowing of large and small airways due to spasm of bronchial smooth muscle, edema and inflammation of the bronchial mucosa,

and production of tenacious mucus. The role of inflammation in the perpetuation of the abnormal airway responses (late-phase reaction) is only now being appreciated. Airways obstruction causes hypoventilation in some lung areas, and continued blood flow to these areas leads to a ventilation/perfusion imbalance resulting in hypoxemia. Arterial hypoxemia is almost always present in attacks severe enough to require medical attention. Hyperventilation occurs early in the attack and results in a decrease in $Paco_2$. As the attack progresses, the patient's capacity to compensate by hyperventilation of unobstructed areas of the lung is further impaired by more extensive airways narrowing and muscular fatigue. Arterial hypoxemia worsens and $Paco_2$ begins to rise, leading to respiratory acidosis. At this point, the patient is said to be in respiratory failure, stage IV of an acute attack (see TABLE 36–1).

Early in the acute attack, there may be just a modest decrease in the maximal midexpiratory flow ($FEF_{25-75\%}$). As the attack progresses, the forced vital capacity (FVC) and the forced expiratory volume during the first second (FEV_1) progressively decrease; associated air trapping and increased residual volume result in hyperinflation of the lungs. Abnormalities in flow rates have been shown to persist *many weeks* after an acute attack.

Mechanisms underlying the bronchoconstriction described above are not well defined. However, an imbalance between β-adrenergic and cholinergic control of airways diameter has been proposed, based on some of the following facts: (1) Increased cholinergic responsiveness is suggested because most asthmatics respond excessively with bronchoconstriction after inhalation of cholinergic agents (eg, methacholine) and because atropine and its derivatives can often partially block irritant-induced bronchoconstriction. (2) There is biochemical evidence of decreased β-adrenergic receptor responsiveness in many asthmatics. Recent studies show decreased numbers of β-receptors in peripheral WBCs of asthmatics compared to controls. The role that treatment with adrenergic drugs may play in the pathogenesis of these findings is still

TABLE 36–1. STAGING OF THE SEVERITY OF AN ACUTE ASTHMA ATTACK.

Stage	Symptoms and Signs	FEV_1 or FVC	pH	Pa_{O_2}	$Paco_2$
I (mild)	Mild dyspnea; diffuse wheezes; adequate air exchange	50–80% of N*	N or Sl. ↑	occasionally N or most often ↓	N or ↓
II (moderate)	Respiratory distress at rest; hyperpnea; use of accessory muscles; marked wheezes; air exchange N or ↓	50% N	N or ↑	↓	generally ↓
III (severe)	Marked respiratory distress; cyanosis; use of accessory muscles; marked wheezes or absent breath sounds; check for pulsus paradoxus 20–30 mm Hg	25% N	Most often ↓	↓	N or ↑
IV (respiratory failure)	Severe respiratory distress; lethargy; confusion; prominent pulsus paradoxus 30–50 mm Hg; use of accessory muscles	10% N	↓↓	↓	↑↑

* N = normal.

unclear. (3) An asthma attack may be provoked by administration of a β-adrenergic blocker. Recently, in about 8% of asthmatics, autoantibodies to the B_2 receptor have been found that may contribute to the severity of asthma.

The observed abnormalities in adrenergic and cholinergic functions in asthma appear to be controlled by the cyclic 3',5'-adenosine monophosphate (cyclic AMP [cAMP])—cyclic 3',5'-guanosine monophosphate (cyclic GMP [cGMP]) systems within various tissues (eg, mast cells, smooth muscle, and mucus-secreting cells). The intracellular concentration of cAMP is a principal determinant of both smooth muscle relaxation and inhibition of IgE-induced release of several chemical mediators: eg, (1) histamine, which causes bronchoconstriction (either directly or by cholinergic reflex action) and increases exocrine secretion, and (2) a low mol wt substance known as eosinophil chemotactic factor of anaphylaxis. Neutrophil chemotactic factor is a mediator of exercise-induced asthma. Leukotrienes (LTC_4, LTD_4, LTE_4), products of the lipoxygenase pathway of arachidonic acid metabolism, are potent bronchoconstrictors that also promote edema and stimulate secretion of mucus. Prostaglandins of the E series and drugs that stimulate β-adrenergic receptors lead to formation of intracellular cAMP and thus inhibit bronchoconstrictive mediator release and cause smooth muscle relaxation. Cholinergic stimulation facilitates mediator release associated with increases in intracellular cGMP.

These mechanisms explain some pathophysiologic aberrations, but the relative importance of each mediator and the degree of autonomic imbalance cannot be defined in an individual asthmatic. However, the concepts are important, because most drugs used to treat asthma have profound effects on the cyclic nucleotide systems.

Pathologic findings in patients who died of status asthmaticus frequently have shown extensive mucus plugs obstructing both large and small airways. The bronchial walls show mucosal edema, thickening of the muscularis layer and basement membrane, and infiltration with eosinophils; mast cells are decreased.

Symptoms and Signs

The symptoms of persons with asthma differ greatly in frequency and degree. Some have an occasional episode that is mild and brief; otherwise they are symptom-free. Others have mild coughing and wheezing much of the time, punctuated by severe exacerbations of symptoms following exposure to known allergens, viral infections, exercise, or nonspecific irritants. Psychosocial stress may precipitate an attack or may be additive with noxious exposures.

Children, in particular, may notice an itching sensation over the anterior neck or upper chest as an early sign of an impending attack, and dry cough, particularly at night and with exercise, may be the sole presenting symptom, especially in children. However, an asthma attack usually begins acutely with paroxysms of wheezing, coughing, and shortness of breath, or insidiously with slowly increasing symptoms and signs of respiratory distress. In either case, the patient usually first notices the onset of dyspnea, tachypnea, cough, and tightness or pressure in the chest, and may even notice audible wheezes. The episode may subside quickly or persist for hours to days. Pulmonary function abnormalities (see under Laboratory Findings, below), may persist for weeks after an acute attack, even in asymptomatic patients.

The cough during an acute attack sounds "tight" and is generally nonproductive of mucus. Except in young children, who rarely expectorate, tenacious mucoid sputum is produced as the attack subsides.

On physical examination during the acute asthmatic attack, the patient exhibits varying degrees of respiratory distress, depending on the severity and duration of the episode. Tachypnea, tachycardia, and audible wheezes are frequently present. Variable degrees of dehydration may occur during prolonged episodes because of sweating and increased insensible water loss from the lungs secondary to tachypnea. The patient

prefers to sit upright or even leans forward, uses accessory muscles of respiration, is anxious, and may appear to struggle for air. Chest examination shows a prolonged expiratory phase with relatively high-pitched wheezes throughout inspiration and most of expiration. The chest may appear quite hyperinflated due to air trapping. Although coarse rhonchi may accompany the wheezes, fine "wet" rales are not heard unless pneumonia, atelectasis, or cardiac decompensation is also present.

In more severe episodes, the patient may be unable to speak more than a few words without stopping for breath. Fatigue and severe distress are evident in rapid, shallow, ineffectual respiratory movements. Cyanosis becomes evident as the attack worsens. Confusion and lethargy may indicate the onset of progressive respiratory failure with CO_2 narcosis. In such individuals, it is not unusual to hear *less* wheezing on auscultation, because the extensive mucous plugging of airways and patient fatigue results in marked reduction of air flow and gas exchange. In an asthmatic with a quiet-sounding chest, an inexperienced examiner may incorrectly attribute the anxiety and respiratory distress to emotional factors or underestimate the severity of obstruction. Such a patient may actually have a more severe problem than a patient with audible wheezes. Extensive small airways obstruction may be present with few auscultatory findings.

Thus, the presence, absence, or prominence of wheezes does not correlate precisely with the severity of an asthma attack. The most reliable signs include the degree of dyspnea at rest, cyanosis, difficulty in talking, pulsus paradoxus of > 20 to 30 mm Hg, and the use of accessory muscles of respiration. The severity of an attack can be most precisely assessed by blood gas determinations.

Between acute attacks, breath sounds may be normal during quiet respiration. However, rales or fine wheezes may be heard during forced expiration or after the patient exercises. Low-grade to moderate wheezing may be heard at any time in some patients, even when the patient claims to be completely asymptomatic. With longstanding severe asthma, especially if dating from childhood, there may be evidence of secondary effects of chronic hyperinflation on the chest wall (eg, "squared off" thorax, anterior bowing of the sternum, and depressed diaphragm).

Complications

Pneumothorax may occur during an acute asthma attack; it presents as a sudden worsening of respiratory distress, accompanied by sharp chest pains and, on physical examination, a shift of the mediastinum. X-ray examination confirms the diagnosis. **Mediastinal and subcutaneous emphysema** due to alveolar rupture and dissection of air along vessels is occasionally observed during an asthmatic attack. **Atelectasis**, usually involving the right middle lobe or even an entire lung, is more common. Unless the collapse involves a substantial amount of lung tissue, the atelectasis is usually only diagnosed as a result of x-ray examination. **Bronchiectasis** is rare. While evidence of acute **cor pulmonale** can occasionally be obtained on an ECG during a severe episode of asthma, chronic cor pulmonale secondary to asthma is rare. Contrary to popular opinion, uncomplicated asthma rarely leads to chronic obstructive emphysema, especially in a nonsmoker.

Laboratory Findings

Blood cell examination: Eosinophilia is commonly present in asthma regardless of whether allergic factors can be shown to have an etiologic role. Blood eosinophilia > 250 to 400 cells/μL is the rule; in many asthmatics, the degree of eosinophilia may correlate with the asthma's severity. The extent to which eosinophilia can be suppressed with corticosteroids (as measured by total eosinophil counts) has been used as an index of the adequacy of dosage of these agents.

Determination of **arterial blood gases and pH** is essential to the adequate evaluation of a patient with asthma of sufficient severity to warrant hospitalization. (See TABLE 36–1 and Ch. 34.)

Sputum in a patient with uncomplicated asthma is highly distinctive. Grossly, it is tenacious, rubbery, and whitish; in the presence of infection, particularly in adults, it may be yellowish. Many eosinophils are found microscopically, frequently arranged in sheets; large numbers of histiocytes and polymorphonuclear leukocytes are also present. Eosinophilic granules from disrupted cells may be seen throughout the sputum smear. Elongated dipyramidal crystals (**Charcot-Leyden**) originating from eosinophils are commonly found. When infection is present, and particularly when there is a bronchitic element, polymorphonuclear leukocytes and bacteria predominate. In uncomplicated asthma, sputum cultures rarely reveal pathogenic bacteria.

Chest x-ray findings vary from normal to hyperinflation. Lung markings are commonly increased, particularly in chronic disease. Atelectasis, most often involving the right middle lobe, is common in children and may be recurrent. Small segmental areas of atelectasis, often observed during acute exacerbations of asthma, may be misinterpreted as pneumonitis. However, the rapidity with which these areas clear suggests atelectasis rather than pneumonitis. An esophagram should be considered part of the evaluation of an infant or young child with suspected asthma to rule out congenital anomalies, which might cause symptoms and signs of airways obstruction. Inspiratory and expiratory chest x-rays are helpful to diagnose foreign-body aspiration as a cause of wheezing in children. The expiratory film will show impairment of exit of air from the affected lung. The expiratory x-rays are especially important in the case of nonopaque foreign bodies.

Pulmonary function tests (see also Ch. 32, above) are valuable in differential diagnosis, and also in known asthmatics to assess the degree of airways obstruction and disturbance in gas exchange, to measure the airways' response to inhaled allergens and chemicals (bronchial provocation testing), to quantify the response to drugs, and for long-term follow-up. Pulmonary function testing is most valuable when performed before and after giving an aerosolized bronchodilator to determine the degree of reversibility of the airways obstruction.

Static lung volumes and capacities reveal various combinations of abnormalities; no abnormalities may be detected in mild cases in remission, however. Of the tests most often used clinically, total lung capacity (**TLC**), functional residual capacity (**FRC**), and residual volume (**RV**) are usually increased. Vital capacity (**VC**) may be normal or decreased.

Dynamic lung volumes and capacities, an index of airways obstruction, are reduced in asthmatics and return towards normal after administration of an aerosolized bronchodilator. In mild, asymptomatic asthmatics, these tests may be normal. Since expiratory flow is determined not only by the diameter of the airways but also by the elastic recoil forces of the lung, flow at high lung volumes will exceed flow at low lung volumes. Tests that measure flow at relatively large lung volumes (forced expiratory volume in 0.5 sec [$FEV_{0.5}$] and peak expiratory flow [PEF] are, to a considerable degree, effort-dependent and are less satisfactory than tests that measure flow over a larger range of lung volume. These include FEV_1 and the mean forced-expiratory flow ($FEF_{25-75\%}$) measured between 25 and 75% of the FVC. The $FEF_{25-75\%}$ is of particular value since it is considered to reflect small airways obstruction. Expiratory flow measurements at large lung volumes are insensitive to changes in peripheral airways resistance and reflect abnormalities principally in central airways. The expiratory flow-volume curve, in which expired lung volume is plotted against flow rate, is probably of greatest value; this curve gives a graphic picture of flow at large and small lung volumes and presumably, therefore, reveals abnormalities in both central and peripheral airways (see FIG. 32-2c above in Ch. 32). In the past, probably too much was made of these distinctions. The FEV_1 provides most of the information needed to manage a patient with asthma.

Distribution of ventilation is frequently abnormal in patients with asthma; ie, various lung units fill and empty asynchronously. This maldistribution is quantified by the

single-breath N_2 test and the 7-min N_2 washout test. Closing volume (CV) is another test for detection of small airways disease; it is increased in asthmatics. Measurements of lung elasticity (lung compliance) in asthmatics, using an esophageal balloon to estimate pleural pressure, have shown a loss of elastic recoil, which is often reversible upon remission. Diffusing capacity for CO (DL_{CO}) is generally normal in asthma; it is low in emphysema (in which there is loss of a functioning alveolar capillary bed with increased lung volume).

Other diagnostic tests: Assessment of etiologic factors is more difficult. Nonspecific irritant factors, particularly cigarette smoke, and evidence of infection (most often viral) should be evaluated. Exacerbations related to environmental allergen exposures, history of rhinitis, or family history of atopic disorders suggests the likelihood of extrinsic allergic factors. Confirmation is best accomplished by an allergy evaluation that includes **allergy skin testing** with extracts to detect IgE antibody to inhalants (pollens, molds, epidermals, house dust) and other allergens (eg, food) suggested by the patient's history. Bronchodilators containing adrenergic agents should be discontinued for 12 h and antihistamines for 48 h, but a corticosteroid may be continued (eg, prednisone up to 40 to 60 mg/day) without interfering with the immediate skin test response. Negative skin test responses to a suitable battery of appropriate allergens strongly rule against an allergic component. Positive skin tests indicate the presence of IgE antibody to the test allergen and represent only the *potential* for allergic reactivity to the allergens in question. Their clinical significance is determined when results are correlated with the pattern of symptoms and related to environmental exposures.

Specific IgE antibody to inhalants may also be detected by a **radioallergosorbent test (RAST)** on the patient's serum, but this test is expensive, subject to laboratory error, and offers little advantage over properly done and interpreted skin tests. Measurement of total serum IgE may be useful in establishing the atopic constitution of the patient. **Inhalational bronchial challenge testing** has been used (1) with allergens to establish the clinical significance of positive skin tests, (2) with methacholine or histamine to assess the degree of airways hyperactivity in known asthmatics, or (3) to aid in diagnosing asthma when the symptoms are atypical. **Exercise testing** using a treadmill or bicycle ergometer has been used, particularly in children, to confirm the diagnosis of asthma in equivocal cases.

Diagnosis and Staging

Asthma should be considered in anyone who wheezes; it is the likeliest diagnosis when typical paroxysmal wheezing starts in childhood or early adulthood and is interspersed with asymptomatic intervals. A family history of allergy or asthma can be elicited in > ½ of asthmatics. Difficulties in diagnosis occur with the initial presentation of asthma, particularly in adults over age 50, or when atypical symptoms (eg, cough without audible wheezing), physical findings, or chest x-rays are noted. A number of other disorders may produce wheezing.

Children with congenital malformations of the vascular system (vascular rings and slings) and of the GI and respiratory tracts (tracheoesophageal fistula) may present with wheezing. The presence of other congenital malformations, special attention to infants whose symptoms begin before age 1 yr, x-ray studies, and a high index of suspicion will lead to a correct diagnosis.

Foreign-body obstruction must be considered, particularly in children with unilateral wheezing or sudden onset of wheezing without a history of respiratory symptoms. Opaque foreign bodies are readily visible on x-ray. With nonopaque foreign bodies, the diagnosis can be established by a history of sudden onset of cough and wheezing in a previously well child, combined with asymmetric diaphragmatic movement or mediastinal shifts on inspiratory and expiratory chest x-rays.

Viral URI involving the epiglottis, glottis, and subglottis generally causes signs and

symptoms of croup (inspiratory stridor, high-pitched cough, and hoarseness) that are distinct from the lower airways signs and symptoms of asthma (see CROUP under VIRAL INFECTIONS in Ch. 191). When epiglottitis is suspected, direct examination of the epiglottis should be performed with great care and with the capability for immediate intubation if acute airways obstruction should develop during examination. Primary bacterial infection of the lower airways, in the absence of underlying predisposing disease, is rare in infants and children. On the other hand, viruses, particularly respiratory syncytial virus, can cause **bronchiolitis** with a clinical picture virtually indistinguishable from asthma during the first 2 yr of life. However, it is rare for an infant or young child to have > 1 to 2 episodes of infectious bronchiolitis, and a history of recurrent episodes of obstructive airways disease should strongly suggest the diagnosis of asthma. Since chronic bronchitis as a primary diagnosis is rare in children, underlying disorders (eg, cystic fibrosis, immunodeficiency disease, and ciliary dyskinesia syndrome) should always be considered. These may be ruled out by a careful history, sweat test, in vivo and in vitro evaluation of immunologic competence, and biopsy of respiratory mucosa with electron microscope study of cilia.

In **adults**, symptoms and signs of airways obstruction due to upper airways involvement may be clarified by determination of a flow-volume curve. Upper airway obstruction due to vocal cord dysfunction may be diagnosed by flexible bronchoscopy during an attack. Chronic obstructive pulmonary disease and heart failure are the main considerations in the differential diagnosis of wheezing, although multiple small pulmonary emboli frequently present with wheezing. Patients with hypersensitivity pneumonitis have a superficial clinical resemblance to asthmatics, but generally have more constitutional symptoms after exposure to the offending substance and typically do not wheeze, except in allergic bronchopulmonary aspergillosis, discussed below in Ch. 43. Patients with bronchial obstructions secondary to malignancy, aortic aneurysm, endobronchial TB, or sarcoidosis may occasionally present with wheezing.

Patients with allergic bronchopulmonary aspergillosis (see also ASPERGILLOSIS in Ch. 9) may present with typical asthmatic symptoms. The diagnosis of aspergillosis is confirmed by the findings of high peripheral blood eosinophilia, immediate skin test reactivity to *Aspergillus* antigen, precipitating antibodies against *Aspergillus* antigen, increased serum IgE concentrations (which appear to fluctuate with the activity of the disease), pulmonary infiltrates (transient or fixed), and a peculiar central type of bronchiectasis.

Other rare disorders that may simulate asthma include carcinoid syndrome, polyarteritis, and eosinophilic pneumonias (including tropical eosinophilia and other parasitic infestations that involve the lung during some phase of the disease). In all, the history is usually sufficiently atypical of asthma to suggest that another disorder is causing the airways obstruction.

Physical examination should search for heart failure and signs of chronic hypoxemia (clubbing of the fingers). Nasal polyposis should suggest aspirin intolerance. Unilateral wheezing should provoke a search for obstruction by a foreign body, vascular malformation, aneurysm, or tumor. In tracheal obstruction, an inspiratory wheeze is present over the upper airway.

Staging of the severity of the asthma attack is critical after the diagnosis is established. This is accomplished by a combination of evaluation of respiratory distress, monitoring of arterial blood gases, and spirometry. TABLE 36–1 illustrates one staging method.

Treatment

Treatment may be conveniently considered as management of the acute attack and day-to-day therapy. Drug therapy enables most patients to lead relatively normal lives with few adverse drug effects. The detailed approach described below is one of a

number that may be tried, but several **general principles** are important regardless of the particular drug or drugs used. (1) Staging of the severity of the attack (see above) is paramount, especially if it has been prolonged (> 12 h) or if the patient is unfamiliar to the examiner. (2) Bronchodilators should be used in orderly progression, with the patient under close observation during the initial therapy. Treatment to alleviate acute respiratory distress without maintenance follow-up treatment often results in a return of acute symptoms within 24 h. (3) Although some asthmatics may benefit from inhalation of nebulized bronchodilators, many cannot inhale the aerosol effectively and require parenteral drugs.

Drug therapy: Five classes of drugs are useful:

1. **β-adrenergic agents** cause bronchial smooth muscle relaxation and modulate inhibition of mediator release, at least in part by stimulating the adenylate cyclase-cAMP system. They include epinephrine, isoproterenol, ephedrine, and some more selective β_2-adrenergic agents (relatively more bronchodilatory β_2 effect and less cardiostimulatory β_1 effect). The latter commonly used β_2-adrenergic agents include metaproterenol, terbutaline, isoetharine, albuterol, and bitolterol. Fenoterol is not yet released in the USA. In general, epinephrine s.c. and one of the inhaled β_2 agents are most useful to treat the acute attack.

2. **Theophylline, a methylxanthine,** relaxes bronchial smooth muscle and modulates mediator release; its mechanism of action is unclear, but it acts as an adenosine antagonist and influences Ca flux across cell membranes and, to a limited extent in vivo, inhibits cAMP phosphodiesterase. Theophylline is a valuable adjunct to adrenergic drugs in the management of acute episodes; many, particularly in the USA, consider it to be the drug of choice for long-term continuous therapy.

3. **Corticosteroids** have multiple mechanisms of action: inhibition of attraction of polymorphonuclear leukocytes to the site of an allergic reaction, stimulation of synthesis of β_2 receptors, and blockage of leukotriene synthesis. While exceptionally effective, systemic corticosteroids are reserved for more difficult cases because of their potential for adverse effects. Short-term use in high dosage (eg, for 5 to 7 days to abort an attack) is unassociated with significant problems. The new generation of surface-active inhaled steroids are very useful for maintenance therapy.

4. **Cromolyn sodium** (disodium cromoglycate—**DSCG**), used prophylactically, appears to inhibit mediator release and reduce airways hyperreactivity. DSCG is primarily useful in children and some adults *for maintenance therapy only and has no place in treatment of the acute attack.* Cost and problems with patient compliance appear to have limited its use in the USA.

5. **Anticholinergic agents** (eg, atropine and its derivative ipratropium bromide) block cholinergic pathways that cause airways obstruction.

Treatment of the Acute Attack

Drug therapy: Patients with acute asthma presenting in Stage I or II (see TABLE 36–1) may be treated effectively with an aerosolized bronchodilator (eg, isoetharine 1% 0.5 mL or metaproterenol 5% 0.3 mL in 2 mL of 0.9% sodium chloride solution) using compressed air for nebulization. Alternatively, epinephrine 1:1000 in a dose of 0.01 mL/kg s.c. up to a maximum of 0.2 mL in children and 0.3 mL in adults, repeated once in 20 to 30 min, if indicated, may be given. Terbutaline, an alternative to epinephrine in the same dosage, is preferred in adults because of somewhat less cardiovascular effect. If there is no response after 2 adrenergic aerosol treatments and/or epinephrine injections, theophylline (as aminophylline) should be given IV.

Different schedules for administering aminophylline are used because individual patients vary in susceptibility to its beneficial or adverse effects. Maintaining serum levels of 10 to 20 μg/mL of theophylline is most effective. Most regimens start with an IV loading dose of 6 mg/kg aminophylline (25 mg/mL, diluted 1:1 with IV fluids) for children or adults given over about 20 min; then a continuous infusion is begun (0.45 mg/kg/h in adults and 1.0 mg/kg/h in children < 12 yr of age). Serum concentrations should be monitored at least q 12 h. If continuous infusion is unfeasible, then giving aminophylline 4 to 6 mg/kg IV over 20 min q 6 h is an acceptable alternative. Arterial blood gases should be obtained, especially if there is no sign of a prompt response (within about 30 min), if the patient is in severe distress or worsening, or if there is uncertainty about what stage the patient is in.

For any patient presenting in Stage III, an arterial blood gas determination should be obtained immediately and aminophylline started IV. For a patient in severe distress, continuous infusion doses may be raised to the limit of 1 mg/kg/h in young or middle-aged adults and 1.25 mg/kg/h in children. Monitoring serum theophylline concentrations is essential to prevent toxicity. Greater caution is necessary and lower dosages (by ½ to ⅓) should be used in patients who have heart failure or liver disease or who are elderly. O_2 at an F_{IO_2} of 40% should be given to correct hypoxemia.

While corticosteroids may be advantageously used in Stage II of an asthma attack, when patients present in Stage III and show no improvement or get worse despite one dose of aminophylline, IV corticosteroids are mandatory. Criteria for hospitalization vary, but definite indications are failure to improve or relapse after repeated adrenergic therapy and aminophylline, and significant decrease in Pa_{O_2} (Pa_{O_2} < 50 mm) or increase in Pa_{CO_2} (Pa_{CO_2} > 50 mm), indicating progression to respiratory failure. Far too many patients with severe asthma attacks are sent home from hospital emergency rooms.

Any patient presenting in or reaching Stage IV should immediately be given hydrocortisone sodium succinate 4 mg/kg IV q 2 to 4 h or methylprednisolone 1 to 2 mg/kg IV q 4 h. IV corticosteroids in these doses (or double the maintenance dose, whichever is greater) are also indicated immediately for any acute asthmatic attack if the patient had taken maintenance corticosteroids any time within the previous 6 to 12 wk.

Patients in Stage IV who show no favorable response to aminophylline and who show evidence of fatigue and progressive deterioration in blood gases and pH should be considered candidates for endotracheal intubation and respiratory assistance. (See Ch. 34.) Such patients should be hospitalized in an intensive care unit (ICU).

Children in Stage III or IV have been given isoproterenol 0.08 to 2.7 μg/kg/min by continuous IV infusion with a suitable infusion pump. This procedure requires ECG and arterial blood gas monitoring in an ICU and supervision by clinicians experienced in monitoring asthmatic children. IV albuterol has been used effectively in England and Canada. It is not available in the USA. Because of the increased potential for arrhythmias in adults, IV isoproterenol should probably not be used.

IV aminophylline and corticosteroids should be continued until the patient's condition has stabilized and there is no danger of progression to respiratory failure. Drugs given orally to a dehydrated, possibly nauseated patient may be erratically delivered to affected tissues. Nebulized bronchodilators (isoetharine or metaproterenol in 1:4 solution in 2 mL of 0.9% sodium chloride solution) may be ineffective in a patient in acute respiratory distress because of the severity of the airways obstruction, but, in some patients, they give short-term relief and may be used q 30 min prn or even more often. Use of continuous nebulization of adrenergic bronchodilators is being investigated. O_2, rather than room air, should be used as the aerosolizing gas. Sedatives and cough suppressants are **contraindicated.**

Anxiety may be extreme, because of hypoxia and the feeling of asphyxiation. Treatment of the underlying respiratory problems, including judicious use of O_2 therapy (see below), is the preferred approach, especially when conducted by calm, attentive, supportive medical personnel.

Fluid and electrolyte balance requires attention, especially when the episode lasts > 12 h, since these patients may be dehydrated. Therapy replaces previous and current fluid losses, not with an arbitrary amount/24 h, but by constant infusion of amounts

sufficient to result in a urine output adequate for the patient's age and size. Overhydration may cause pulmonary edema. Humidification of inhaled air or O_2 reduces excess respiratory tract loss.

With progressive severity and duration of the episode, respiratory acidosis may supervene; the arterial pH may drop alarmingly to ranges of pH 7 to 7.1. Most adults are intubated at this stage and started on assisted ventilation, because *the acidosis mainly reflects a respiratory mechanical problem that must be relieved.* Use of alkaline solutions (eg, sodium bicarbonate) in the IV fluid should be limited to maintain the pH between 7.2 and 7.3, since there is some evidence that adrenergic agent resistance is reversed by normalizing the pH. While there are theoretic objections to adding bicarbonate to a closed system, sodium bicarbonate has been safely and successfully used in children with status asthmaticus. It should be used only with careful blood gas and pH monitoring.

Supplemental K may need to be added to the infusion, since K shifts occur with changes in arterial and tissue pH and fluid turnover in a dehydrated patient. In addition, high doses of hydrocortisone more so than methylprednisolone given during therapy promote urinary K loss.

O_2 therapy is always indicated, since severe asthmatics are invariably hypoxemic. The inspired O_2 concentration (F_{IO_2}) is guided by blood gas levels; P_{aO_2} should be maintained > 60 mm Hg, preferably in the 70 to 90 mm range, if possible. O_2 may be given effectively with nasal prongs or, if tolerated, a Venturi mask. In the occasional patient who will not tolerate a mask, use of nasal prongs with low O_2 flow (2 to 4 L/min) may achieve the same result. Since O_2 may be drying to the respiratory mucosa, it should always be humidified.

Respiratory tract infections exacerbating asthma are predominantly viral; bacterial infections rarely play a significant role, especially in children. However, if the patient expectorates yellowish, green, or brown sputum, and Wright's stain of the sputum shows a predominance of polymorphonuclear WBCs, antibacterial therapy is given empirically. This is especially appropriate in adults with a known tendency to have chronic or recurrent bronchitis. The antibiotic should be chosen according to bacteriologic findings, but ampicillin is usually most useful. If the patient is allergic to β-lactam antibiotics, erythromycin or tetracycline (the latter should not be given to young children) may be given. Gram stain of the sputum, noting intracellular bacteria, and chest x-rays are useful guides to therapy.

Although not all physicians agree, many believe that **chest x-ray** is mandatory in all hospitalized asthmatics. Spontaneous pneumothorax and subcutaneous and mediastinal emphysema are complications of acute asthma, particularly in children. A large pneumothorax requires immediate treatment. Mediastinal and subcutaneous emphysema rarely cause difficulty, even when large. Rarely, compression of the glottis may occur with extreme extravasation of air into the soft tissues of the neck.

Maintenance Therapy of Asthma

Following an acute asthma attack, oral drugs should be continued for 2 to 4 wk even if the patient is asymptomatic, because pulmonary function abnormalities and hypoxemia may persist for this long. Several types of treatment are described below with the understanding that more than one approach may be used. Patients with mild asthma and infrequent episodes of wheezing may need therapy only intermittently when symptomatic. Others with more persistent symptoms benefit from continuous around-the-clock treatment.

Cromolyn sodium, 1 capsule (20 mg) q 6 h via an inhaler, or with cromolyn solution and a pressure-driven nebulizer, is most useful in children; it may avoid the need for corticosteroids or may enable a reduction in their maintenance dosage. While some physicians use cromolyn as a first-line maintenance drug for chronic asthma, in the USA it is often used in patients who do not respond satisfactorily to theophylline and adrenergic drugs; it should be tried before starting corticosteroids. *The drug is not a bronchodilator, has no place in treating an acute asthma attack, and is used only prophylactically.* It is effective in preventing exercise-induced asthma: Administration immediately before exercise blocks an attack (the most effective drug for this purpose is an inhaled adrenergic agent). Patients with either extrinsic or intrinsic asthma may respond favorably, although the likelihood is greater with extrinsic asthma. The drug is generally stopped during an exacerbation, since, in this instance, it may act as an airways irritant.

Bronchodilators: A variety of oral theophylline formulations are available as tablets, capsules, or liquids. Anhydrous preparations are preferred to theophylline combinations. Sustained-release (SR) formulations maintain serum theophylline concentration in the therapeutic range when given tid, bid, or even once/day in particularly slow theophylline metabolizers. Since children, in particular, metabolize theophylline rapidly, serum concentration peaks (which may cause toxic symptoms) and troughs (which may be therapeutically ineffective), often occur with the conventional rapidly absorbed formulations. SR formulations overcome this problem and are convenient for adults and older children. Because capsules may be opened and the pellet contents mixed with moist food, they are very useful in young children. Neither tablets nor pellets should be chewed. As with IV administration, toxic symptoms may be observed at concentrations > 20 μg/mL. Nausea, vomiting, and CNS stimulation should be watched for, serum theophylline measured, and the dosage or interval modified accordingly.

With adequate doses of theophylline, further improvement can occasionally be gained by adding one of the newer β_2-adrenergic bronchodilators. Ephedrine, formerly a mainstay of therapy, frequently caused undesirable side effects and is rarely used today. Metered dose inhalers (MDI) that contain terbutaline, metaproterenol, albuterol, fenoterol, or bitolterol give bronchodilator effect for 4 to 6 h. *Patients should be cautioned about overuse of MDI.* The average MDI provides 200 doses and should last 4 wk. A variety of "spacers" or holding chambers are available for use by young children or adults who are unable to use the MDIs properly. Adrenergic aerosols with a pressure-driven nebulizer can be used at home advantageously in children too young to use an MDI. Often cromolyn solution (2 mL unit dose) is mixed with the adrenergic drug (eg, 0.5 mL isoetharine) in the nebulizer. The significance of a poor, short-lived response to several inhalations of adrenergic agents must be understood by the patient as an indication to seek medical attention.

Alternatively, terbutaline 2.5 to 5 mg orally qid can be given to supplement theophylline therapy, but adverse side effects of the β_2-selective agents are more evident with oral drugs than aerosols. Hand tremor, the most commonly observed adverse β_2-effect, becomes much less troublesome with continuous administration of the drug as tolerance develops. These drugs should be used cautiously in patients with a history of cardiac arrhythmias or hyperthyroidism.

When there is no satisfactory response to theophylline and a β_2-adrenergic agent, a corticosteroid should be added; short-term use of high doses frequently relieves exacerbations. Prednisone 40 to 60 mg/day orally in adults or 1 to 2 mg/kg/day in children (either divided or given as a single dose in the early morning) should be maintained for 5 to 7 days, after which the patient is reevaluated. Some patients may require 7 days more to achieve maximum benefit; then the prednisone dosage can be reduced by 50% decrements q 2 days until the drug is discontinued or the lowest dose that maintains good control of symptoms is reached. If prednisone cannot be discontinued without the appearance of an unacceptable degree of symptoms, it may be worthwhile to attempt alternate-day therapy with prednisone or another short-acting corticosteroid, beginning with double the previous daily dose given as a single dose before 8 AM q 48 h. If the patient does well, an attempt is made to reduce the dose by 5 mg q 10 to 14

days. Side effects are minimized with alternate-day therapy, but satisfactory asthma control may be difficult to achieve in adults. Daily doses should be reinstituted during an exacerbation.

Beclomethasone, triamcinolone acetonide, and flunisolide represent a new generation of aerosol corticosteroids with potent surface activity and offer a major advance in long-term maintenance therapy (supplemental systemic corticosteroids are necessary for an acute attack). They control asthma, with minimal adverse effects, in doses from 400 to 800 μg/day. However, when chronic steroid-dependent asthmatics are converted to aerosols from systemic corticosteroids, *an inadequate hypothalamic-pituitary-adrenal axis response to stress may occur that may require resumption of systemic corticosteroids.* When patients are converted from oral to inhaled steroids, flaring of allergic rhinitis or eczema may occur and is further evidence of a lack of systemic effect of the aerosolized agent. *Candida albicans* has been cultured from the nasopharynx of patients on topical steroid aerosol therapy, but it rarely causes disease.

Ipratroprium bromide is being used successfully as an inhaled bronchodilator alone, or in combination with an adrenergic agent or theophylline in the management of both acute and chronic asthma. It is not yet available in the USA.

The role that extrinsic factors (generally animal danders, dust, airborne molds, and pollens) play in the disease should be rigorously investigated. If suspected, allergy skin tests should be done to confirm the history. Allergens that can be controlled by avoidance (animal danders, house dust mite) should be eliminated. Other allergens (dust mite, mold, and pollens) may be selected for a trial of allergy immunotherapy (formerly "hyposensitization"). Improvement should be noted within 12 to 24 mo after beginning treatment. If no significant improvement is noted within this period, therapy should be discontinued. When improvement occurs, the optimum duration of therapy is unknown, but at least 3 yr is recommended.

Nonspecific exacerbating factors (eg, cigarette smoke especially, odors, irritant fumes, and changes in temperature, atmospheric pressure, and humidity) should also be investigated and controlled when possible. Aspirin should be avoided, particularly by patients with nasal polyposis, because of a significant incidence of aspirin-induced asthma. A few aspirin-intolerant asthmatics also react adversely to indomethacin, and rarely to tartrazine (FD and C yellow No. 5). Sensitivity to sulfites (used widely as food preservatives) is suggested by asthma attacks that follow eating from a salad bar or drinking red wine or beer.

Surgical procedures should be performed when the patient's pulmonary state is optimum. Corticosteroids may be required; short-term use is less hazardous than a compromised respiratory status. Procedures involving nasal and tracheal manipulation are particularly troublesome and polypectomies in aspirin-sensitive asthmatics may require a week's pretreatment with prednisone 50 to 60 mg/day orally.

ACUTE BRONCHITIS

Acute inflammation of the tracheobronchial tree, generally self-limited and with eventual complete healing and return of function. Though commonly mild, bronchitis may be serious in debilitated patients and in those with chronic lung or heart disease. Pneumonia is a critical complication.

Etiology

Acute infectious bronchitis, most prevalent in winter, is often part of an acute URI. It may develop after a common cold or other viral infection of the nasopharynx, throat, or tracheobronchial tree, often with secondary bacterial infection. Exposure to air pollutants and, possibly, chilling, fatigue, and malnutrition are predisposing or contributory factors. Recurrent attacks often complicate chronic bronchopulmonary dis-